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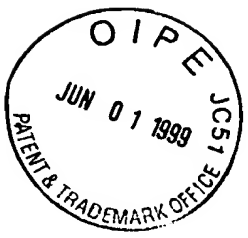

EXHIBIT B

Enclosure 2

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Pharmacology of an extract of salai guggal ex-*Boswellia serrata*, a new non-steroidal anti-inflammatory agent

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Abstract

Pharmacological evaluation of alcoholic extract of salai guggal (AESG) has been carried out in experimental animals. AESG displayed marked anti-inflammatory activity in carrageenan induced oedema in rats and mice and dextran oedema in rats. It was equally effective in adrenalectomized rats. In formaldehyde and adjuvant arthritis, AESG produced prominent anti-arthritic activity but no significant effect was observed in cotton pellet-induced granuloma test. It inhibited inflammation induced increase in serum transaminase levels and leucocyte counts but lacked any analgesic or anti-pyretic effects. The gestation period or parturition time in pregnant rats or onset time of castor oil-induced diarrhoea was unaffected by AESG and no significant effect was seen on cardiovascular, respiratory and central nervous system functions. No ulcerogenic effects were found in the rat stomach. The oral and intraperitoneal LD_{50} was greater than 2 g/Kg in mice and rats.

Introduction

Anti-inflammatory drugs presently available for the treatment of various inflammatory disorders have one or the other adverse and undesirable side effects. Therefore, an attempt was made to search for herbal based anti-inflammatory products reputed to have beneficial effects for rheumatic disorders in folklore medicament.

Boswellia serrata (N.O. Burseraceae), a large branching tree, grows abundantly in dry hilly parts of India. The gum resin exudate of *Boswellia serrata* is known as salai guggal in the vernacular and is used in Ayurvedic system of medicine for the treatment of rheumatism, obesity and various other disorders [1]. Chemically it is reported to contain gum, resin, terpenoids and essential oils [2–6]. A non-phenolic fraction obtained from its gum resin is reported to possess analgesic and psychopharmacological effects [7].

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In view of these reports, pharmacological investigations of different solvent fractions of salai guggal were undertaken. The alcohol (95% v/v) extracted fraction of salai guggal (AESG) revealed it to possess marked anti-inflammatory, anti-arthritic and anti-hyperlipidemic activities. The present communication describes the anti-inflammatory and anti-arthritic activity. Part of this work has been reported at the April 1981 meeting of the British Pharmacological Society.

Material

After cleaning the gum resin (1 Kg) from the extraneous material it was defatted with petroleum ether at room temperature (24°C). Three such extractions with petroleum ether (60–80°C) gave about 40% of the mass comprising of fatty material and essential oil. The residue (marc) 580 g after drying was subjected to percolation with ethanol (95% v/v) at 24°C for 48 hours. The extract was concentrated under vacuum to give a cream colour powder (125 g) which constituted 12.5% of the original mass of the alcohol extracted residue has been shown to comprise a mixture of triterpene pentacyclic acid derivatives of boswellic acid, the major single component of which is β-boswellic acid to the tune of 30%.

Methods

Male albino Charles Foster rats (110–160 g) and albino mice (18–25 g), of either sex were employed for this study at room temperature of 24 ± 1°C. Drugs were prepared as fine homogenised suspension in 2% gum acacia for administration.

Anti-inflammatory activity

Rats and mice in groups of 5–10 animals for each dose were employed. The test compounds were administered orally 1 hour prior to induction of oedema in acute tests and once daily in chronic tests. In each experiment one group served as a control and was given only vehicle (2% gum acacia) and another group was given a standard anti-inflammatory drug Phenylbutazone (PNB) for comparison. Results were calculated as per cent inhibition as compared with control group.

The significance of drug induced changes was estimated using Student 't' test.

Carrageenan-induced oedema in rats

Oedema in the left hind paw of rat was induced by injecting 0.1 ml of carrageenan (1% w/v) solution in normal saline into the limb after 1 hour of the drug treatment P.O. [8]. The volume of paw oedema was measured with a volume differential meter model 7101 UGO Basile immediately and 4 hours after carrageenan injection.

Dextran-induced oedema in rats

0.1 ml of dextran (6% w/v) solution was injected into the plantar surface of the paw 1 hour post-drug treatment P.O. [9]. Final paw volume was measured 1 h later.

Carrageenan-induced oedema in adrenalectomised rats

Adrenalectomy was performed in rats [10]. Normal saline was made freely available instead of water. Two days after the surgery, experiments were performed by injecting carrageenan as described above.

Carrageenan-induced oedema in mice

Oedema was induced in the left hind paw of the mice by injecting 0.05 ml of 1% carrageenan solution in normal saline 1 hour post drug treatment P.O. [11]. 4 h after carrageenan injection, the animals were killed by decapitation and both hind paws were cut at the ankle. The oedema was calculated by subtracting the weight of the control limb from that of the injected limb.

Formaldehyde-induced arthritis in rats

Arthritis was induced in this test by injecting 0.1 ml of formaldehyde (2% v/v) in normal saline in the region of subplantar on the 1st and 3rd day of experiment [12]. Paw volume was measured before formaldehyde injection and once every day for ten days and drugs were administered P.O. daily. The oedema of the paw in each group was calculated and expressed as per cent inhibition compared to control untreated group.

Cotton pellet test

Autoclaved cotton pellets 50 ± 1 mg were implanted under each axilla and groin region of ether anaesthetised rats [13]. Drug was administered P.O. daily once a day for seven days. Rats were sacrificed on 7th day and the pellets along with surrounding granuloma tissue were taken out and dried in oven at 60°C and weighed.

Adjuvant-induced developing arthritis in rats

Arthritis was caused by injecting 0.05 ml of (0.5% w/v) suspension of killed *Mycobacterium tuberculosis* (Difco), homogenised in liquid paraffin in the left hind foot [14]. The administration of the test drug and phenylbutazone orally was started one day before the injection of Mycobacterium and continued till day 14. Paw volume was measured on alternate days and per cent inhibition was calculated on day 14.

Adjuvant-induced established arthritis in rats

Adjuvant arthritis was induced as described above and the rats were left untreated until the 14th day [15]. The animals with no clear secondary lesions if any were discarded and the remainder selected into groups of five and were given treatment with test drug or PNB orally beginning on day 14 and terminating on day 28. Foot volumes were measured on alternate days.

Effect on serum transaminases in rats

Formaldehyde arthritis was induced as described above with one group not receiving formaldehyde to act as control. Test drugs were administered P.O. daily for 7 days and the rats killed on the 8th day. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were evaluated [16].

Ulcerogenic index in rats

Drugs were administered P.O. daily for six days and the food was withdrawn from 2 h before and 2 h after the drug treatment. Water was supplied freely. The animals were sacrificed on the 7th day; the stomach removed, cut along the lesser curvature and gastric contents removed; stomachs were washed with saline and examined under the dissecting microscope (20 ×) for signs of ulceration. The degree of single ulceration was determined for each stomach examined and scored according to the method described by THUILLIER et al. [17].

Analgesic activity in mice

Antagonism of acetic acid induced writhing

Mice of either sex in groups of ten were administered 10 ml/kg of acetic acid (3% v/v) by intraperitoneal injection [18]. Test drug was administered orally 30 min before the injection of acetic acid. The animals were observed for appearance of writhing syndrome. The percent of mice protected in each group was calculated.

Haffner's tail clip method

Mice given graded doses of test drug orally in increasing order were observed for reaction of pain due to application of clip at the base of tail [19].

Anti-pyretic activity

Pyrexia was produced in rats by injection of 2.0 ml of yeast (15% w/v) suspension in (2% w/v) gum acacia [8]. Drugs were administered orally after 16 h when the temperature increase was at its peak. Body temperature was measured with a telethermometer Type FM6 at hourly intervals over the succeeding 4 h.

Diuretic activity

Graded doses of drugs were orally administered to 24 h fasted rats along with tap water (25 ml/kg body weight) [21]. Controls rats were administered equivalent volumes of vehicle in water. Animals were kept in metabolic cages and urine was collected over a 5 h period.

Effect on gross observation and acute toxicity in mice

Increasing doses of test drug were administered orally to group of 10 animals housed in transparent perspex observation chambers [22]. The animals were continuously observed for 2 h and then at half hourly intervals for the next 6 h for any change in spontaneous motor activity, reactivity, muscle tone, gait, respiration and ptosis etc. Mortality was recorded over 72 h.

Effect on cardiovascular system and respiration in anaesthetised dogs

Mongrel dogs of either sex (8–12 kg body weight) were

anaesthetised with pentobarbitone sodium (35 mg/kg i.p.). Carotid blood pressure, heart rate and respiration were recorded on Grass model polygraph model 7D [23]. Drugs were administered through a venous canula or intraduodenally through polythene canula placed in the duodenum. Responses to adrenaline (2–3 μg), noradrenaline (1–2 μg), carotid artery occlusion for 45 sec acetylcholine (2–4 μg), histamine (2–4 μg) and isoprenaline (0.5–1 μg) were recorded both before and after graded doses of administered drug.

Effect on smooth muscle preparations in vivo

Effect on gestation period, parturition, litter size and post partum bleeding in rats

Female rats in the 18–21st day of gestation were obtained and maintained individually in separate cages with bedding of wood shavings [24]. Drugs were administered orally twice daily to groups of 10 rats for each dose levels for 1–4 days and one untreated group was used as a control. The animals were kept under close observation during the day time and the time of parturition was recorded as evidenced by the birth of first pup or initiation of excessive bleeding from vaginal opening. 4–25 h after the beginning of parturition the dams were sacrificed and the uteri examined. Animals that gave birth during the night were observed for 4 h the following day before they were sacrificed so that all dams were allowed at least 4 h from the beginning of parturition to give birth to their offsprings.

Effect on castor-oil-induced diarrhoea in rats

Overnight fasted rats were placed in groups of 5 and were administered graded doses of test drugs P.O. and 1 h later castor oil (10 mg/kg body weight) was administered orally [25]. The animals were observed for onset time and characteristic of diarrhoea.

Results

Alcoholic extract of salai guggal (AESG) in a dose range of 50–200 mg/kg orally produced marked inhibition of carrageenan-induced paw oedema in rat and formaldehyde arthritis swelling in rats (Table 1). In adrenalectomised rats, the inhibitory effect of AESG on carrageenan oedema was found to be similar to that of rats with intact adrenals (Table 1). It failed to show any effect on cotton pellet test. In chronic test of developing adjuvant arthritis in rats, AESG (50–200 mg/kg orally) displayed prominent anti-arthritic activity with marked inhibition of secondary lesions and loss in body weight as compared to PNB (Table 2). In established adjuvant arthritis in rats, AESG and PNB at 100 mg/kg orally caused reduction in swelling by 45% and 51% respectively (P-value < 0.05).

AESG in doses of 50 and 100 mg/kg orally and PNB at 100 mg/kg P.O. inhibited the inflammation induced increase in SGPT and SGOT levels (Fig. 1). Like PNB, it lowered the total leucocyte count. AESG at 50 and 100 mg/kg orally inhibited the total leucocyte count by 56.62% and 65.62% (P-value < 0.01) respectively whereas PNB at 100 mg/kg P.O. inhibited by 69.32% (P-value < 0.01). It did not show any ulcerogenic activity in rat stomach in doses as high as 1 g/kg orally, a point of distinct advantage whereas the ulcerogenic index with PNB was found to be significantly high (1.75 with P-value < 0.01). It does not possess any analgesic or antipyretic or diuretic effect in doses of 50–200 mg/kg orally. Graded doses of AESG up to 2 g/kg orally revealed no change in general behaviour in rats and mice and no mortality could be detected.

Table 1

Inhibitory effect of AESG and PNB in carrageenan and dextran-induced oedema and formaldehyde arthritis.

Treatment	Dose mg/kg p.o.	Carrageenan* oedema (ml)	Carrageenan** oedema (ml) (adrenal-ectomised)	Dextran** oedema (ml)	Carrageenan*** oedema (mg)	Formaldehyde** arthritis swelling (ml)
Control	—	0.84 ± 0.02	0.98 ± 0.06	1.05 ± 0.02	50.2 ± 3.06	0.46 ± 0.07
AESG	50	0.51 ± 0.13[a] (39)	0.57 ± 0.03[a] (42)	0.75 ± 0.04[a] (29)	40.8 ± 4.21 (19)	0.25 ± 0.03[a] (46)
	100	0.32 ± 0.03[a] (62)	0.39 ± 0.05[a] (60)	0.65 ± 0.06[a] (38)	32.4 ± 3.08[a] (35)	0.18 ± 0.06[a] (61)
	200	0.23 ± 0.04[a] (73)	—	0.55 ± 0.02[a] (48)	28.0 ± 2.98[a] (44)	0.12 ± 0.04[a] (74)
PNB	50	0.44 ± 0.11[a] (48)	—	—	34.0 ± 3.98[a] (32)	0.21 ± 0.06[a] (54)
	100	0.35 ± 0.03[a] (58)	0.50 ± 0.04[a] (55)	— (52)	0.15 ± 0.08[a]	(67)

Alcoholic extract of salai guggal (AESG), Phenylbutazone (PNB).
* = 10 rats per group, ** = 5 rats per group, *** = 10 mice per group. Results are mean ± standard error (S.E.) with % inhibition shown in parentheses.
p-value, [a] $p < 0.01$; [b] $p < 0.02$, [c] $p < 0.001$.

Table 2
Effect of AESG and PNB on adjuvant-induced arthritis in groups of 10 rats.

Treatment	Dose mg/kg p.o.	Swelling (ml) mean ± s.e.	% Inhibition	Secondary lesions	Change in body weight (g) mean ± s.e.
Control	—	1.49 ± 0.03	—	Severe	−46 ± 5.5
AESG	50	0.97 ± 0.03**	34.89	Mild	−20 ± 3.0**
	100	0.75 ± 0.05**	49.66	Mild	−14 ± 4.3**
	200	0.62 ± 0.04**	58.38	Mild	−9 ± 2.2**
PNB	50	1.10 ± 0.03**	26.17	Moderate	−29 ± 3.2*
	100	0.60 ± 0.02**	59.73	Mild	−16 ± 2.6**

p-value, * $p < 0.01$, ** $p < 0.001$.

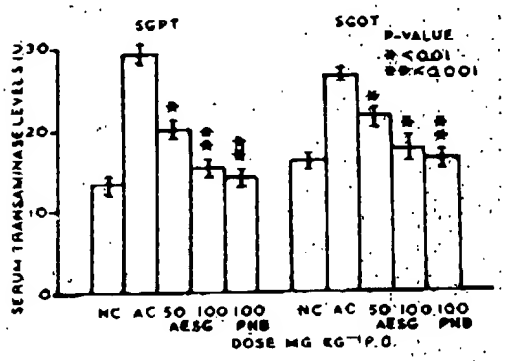

Figure 1
Inhibitory effect of alcoholic extract of salai guggal (AESG) at 50 and 100 mg/kg and Phenylbutazone (PNB) at 100 mg/kg on oral administration on elevated serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) levels in formaldehyde induced arthritis. NC, Normal control without arthritis; AC, arthritis control; Each bar represents the mean ± s.e. of 5 animals in each group. One unit of the enzyme activity was equivalent to the formation of 0.047 ωg pyruvic/min/ml.

over a period of 72 hours. It did not show any effect on B.P., heart rate and responses to various autonomic agents and respiration when administered intravenously up to 100 mg/kg or intraduodenally up to 500 mg/kg. Aspirin at 50 mg/kg orally prolonged the gestation period by 1–2 days, parturition by 2–6 hours and caused excessive post partum bleeding and also affected the number of alive litters born to pregnant rats. No such effects were observed with AESG administration even in 200 mg/kg orally. In castor oil-induced diarrhoea in rats, administration of AESG (50–200 mg/kg orally) failed to prolong the onset of diarrhoea whereas PNB at 100 mg/kg orally significantly delayed the onset of diarrhoea by 56% (P-value < 0.001).

Discussion

Alcoholic extract of salai guggal (AESG) is a new potent anti-inflammatory and anti-arthritic agent with remarkable activity as evidenced by its effectiveness in several acute and chronic experimental test models of inflammation. It reduced the carrageenan-induced paw oedema in rats and mice and dextran-induced oedema in rats. The importance of the former test in rats resides in its sensitivity to the anti-inflammatory drugs of proven value [26]. It produced marked inhibitory effect in formaldehyde arthritis but failed to show any effect in cotton pellet-induced granuloma test which is acknowledged to be more sensitive to steroidal type of drugs and non-steroidal anti-inflammatory drugs (NSAID's) show weak activity in this test [27]. Like phenylbutazone it also inhibited the SGOT and SGPT rise which occurs in prolonged inflammatory disorders. In chronic test of adjuvant developing and established arthritis, AESG displayed prominent arthritic activity. The effectiveness of AESG in the established arthritis indicates its possible usefulness as a therapeutic agent. It also reduced the rate of loss of body weight, occurrence of secondary lesions – haemorrhagic patches on the ears, nodules on the tail and swelling of uninjected limbs. It does not possess any analgesic or antipyretic activities. It is free from any effect on central nervous and cardiovascular systems. The anti-inflammatory activity of AESG does not appear to be mediated through the pituitary-adrenal axis since it is not significantly altered by adrenalectomy.

NSAID's frequently cause gastrointestinal tract disorders as a common side effect and strong correlation between the potency of NSAID as an inhibitor of PG synthesis and as an irritant of gastrointestinal tract has been suggested [28–30].

Inhibition of prostaglandin (PG) synthetase is proposed as a common mechanism of the NSAID's [31]. In general most of the NSAID's have well balanced anti-inflammatory, analgesic and antipyretic and ulcerogenic activities which are considered to be due to PG synthetase inhibitor activity. AESG like other NSAID's possess marked anti-inflammatory activity. Its freedom from analgesic, antipyretic and particularly ulcerogenic effects in the rat stomach are suggestive that AESG does not seem to act mainly by inhibitory effect on PG synthetase. This is further supported by its inability to prolong gestation period in pregnant rats or to delay in onset time of castor oil induced diarrhoea in rats which have been reported almost due to inhibition of PG synthesis [32, 33, 25].

Preclinical acute toxicity study in mice and rats, sub-acute toxicity in rabbits for 3 months and chronic toxicity in primates for 6 months revealed AESG to be safe. Clinical trials study conducted in Jammu Medical College on patients of arthritis and allied disorders revealed AESG to possess promising therapeutic effects (Unpublished observation).

In summary AESG is a new non-steroidal anti-inflammatory and anti-arthritic drug with distinct advantage of its freedom from gastric ulcerogenic effects. Based on this research work, an ethical herbal preparation is being marketed in India.

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